REMARKS

The Office Action of July 28, 2004 presents the examination of claims 1-179. These claims are canceled, being replaced by the present claims 180-222. This method of amendment was chosen for its editorial simplicity.

Support for the new claims

The present claims are directed to the subject matter of the prior claims 1-179. In general, the recitations of the claims are similar to those of the original claims. The present claims are organized as a set directed to chimeric viruses, and an immunogenic composition comprising one of those viruses, and as a set of isolated polynucleotides, and methods for making the viruses by expression of one of those polynucleotides or a vector comprising one of those polynucleotides.

New claim 180 is directed to a chimeric parainfluenza virus (PIV) that includes a partial or complete PIV genome or antigenome combined with one or more heterologous gene(s) or genome segment(s) encoding a complete open reading frame or one or more antigenic determinant(s) of one or more heterologous pathogen(s) operably linked to regulatory sequences operable in said PIV genome or antigenome to form a chimeric PIV genome or antigenome. This feature of the invention is described at e.g. page 43, lines 29-33, page 47, lines 22-34 and page 63, lines 8-9.

The partial or complete PIV genome or antigenome also includes a polynucleotide encoding a wild-type L protein of the PIV. The Examiner should note that many of the working examples retain the L protein of the background virus into which the heterologous genes are introduced. See, for example, Figures 1A and 11. See also, p. 69, lines 9-17 (any segment can be interchanged "singly or in combination with one or more other BPIV genes"; in general "the HPIV3 gene(s) or genome segment(s) selected for inclusion ... will include one or more of the HPIV ... HN or F glycoproteins.") That is, the BPIV L gene remains in the construct with the BPIV backbone.

Furthermore, the infectious chimeric PIV is attenuated for replication at least 10-fold in the respiratory tract of a primate host infected with said chimeric PIV. This feature of the invention is described at, e.g. page 87, lines 26-29.

New claim 181 recites that the heterologous gene or genome segment is inserted into the PIV genome or antigenome at one or more site(s) selected from the group consisting of a site between the P and M open reading frames, a site between the N and P open reading frames, a site between the HN and L open reading frames and a site between the 3' leader and the N open reading frame.

Figure 11 shows the effect of the site of insertion into different sites upon attenuation *in vitro*. Table 13 at p. 137 presents *in vivo* data. Table 2 (p. 105) shows weaker effects *in vivo* (0.5 to 1.5 log units) for inserting just a measles HA gene into NP, PM and HNL sites of HPIV3. Table 10 at p. 126 shows insertion into NH-L site allows tailoring of attenuation *in vivo* according to insert length. Figure 13 (and p. 38, lines 8-10) shows insertion into a site between the 3' leader and N ORF.

New claim 182 lists the point mutations that may be introduced from the mutant HPIV3 strain cp45 as additional mutations. These specific mutations are described at, e.g. page 35, line 1 to page 36, line 12.

New claim 189 recites that the L protein gene of the chimeric virus encodes a mutation at the amino acid position corresponding to amino acid 456 in the L protein of HPIV3. This feature of the invention is described at page 58, lines 1-8.

New claim 196 recites that the chimeric genome or antigenome includes a plurality of inserts of genome segments operably linked to gene start (GS) and gene end (GE) signals from the PIV genome into which the gene segments are inserted, with the result that at least a stated degree of attenuation is obtained. This is described at, e.g. 80, lines 7-8. See also, the constructs illustrated by Figures 1A-1B, 6A and 10, and the descriptions thereof at pp. 31-32, 35 and 36-37, respectively. See also page 26, lines 13-14, describing substitution of one open reading frame for another.

Several dependent claims recite that a glycoprotein gene or open reading frame thereof is introduced into the chimeric PIV. Such is described at, e.g. page 45, lines 19 ff.

Embodiments of the invention as sub-viral particles are described at, e.g. page 21, line 17.

The corresponding claims related to isolated polynucleotides are similarly supported.

Substance of the Interview

A personal interview with the Examiner and her Supervisor was held on July 13, 2005 and a further telephone discussion with the Examiner was held later that day. Applicants wish to thank the Examiner and her Supervisor very much for providing so much of their time to help resolve the issues in this matter.

Applicants first addressed the Collins and Klein references of record. Applicants explained that Collins (US 6,264,957) is not citable to support an obviousness rejection, being prior art only under 35 USC section 102(e) and subject to common ownership with the present application at the time the invention was made. Klein was explained as irrelevant to the present invention, being directed to producing subunit vaccines that are composed of proteins expressed in *in vitro* cultures.

Applicants presented proposed claim amendments that were considered by the Examiner and further explained how the amended claims were patentable over the Belshe reference (US 5,869,036). The Examiner or her supervisor provided some comment upon the proposed claims, such comments generally being limited to suggestions for avoiding possible rejections for lack of written description. It was acknowledged that Applicants' proposed claims, which are reflected in the claims presented in this paper and include the suggestions of the Examiner or her Supervisor, would likely be considered to distinguish the invention over Belshe.

The Examiner also agreed that claims to embodiments of chimeric viruses, immunogenic compositions comprising such viruses, isolated polynucleotides constituting the genomes of such viruses, expression vectors constituting such polynucleotides, methods for making the chimeric viruses, and methods for immunization using the viruses, would all be examined in the present application if presented.

Issues raised in the Office Action

The Office Action of July 28, 2004 presents the minor issue of claim 57 being formed of two sentences. This is moot in view of cancellation of claim 57.

Claims 1-25, 28-29, 32-34, 38-65, 74-77, 80-86, 90-91, 95-97, 122 and 127-137 are rejected under 35 U.S.C. § 102(e) as being anticipated by Belshe et al. U.S. 5,869,036. Claims 1-98 and 122-137 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Belshe in view of Collins et al. (U.S. 6,264,957) and Klein et al. (WO93/14207). Claims 1-98 and 122-137 are provisionally rejected under the judicially-created doctrine of obviousness-type double patenting over claims 1-67 of the copending application 09/586,479. Claims 1-24, 32-34, 38-39, 82-88, 95-98, and 122-137 are provisionally rejected under the judicially-created doctrine of obviousness-type double patenting over claims 1-30 and 46-55 of the copending application 09/459,062. Claims 1-24, 32-34, 38-39, 82-88, 95-98, and 122-137 are provisionally rejected under the judicially-created doctrine of obviousness-type double patenting over claims 8-12, 15-16, 18-22, 24-26, 34-39 and 40 of the copending application 09/458,813. Finally, claims 1-98 and 122-137 are provisionally rejected under the judicially-created doctrine of obviousness-type double patenting over claims 1-67 of copending application no. 10/030,544.

All of the above rejections are moot in view of the substitution of the present claims 180--222 for the prior claims 1-179. Applicants submit that the above-stated rejections should not be applied against the present claims 180-222.

Rejections for double patenting

The application no. 10/030,544 has been abandoned, rendering moot the rejection under the judicially-created doctrine of obviousness-type double patenting over claims 1-67 of this application. However, it appears to Applicants' Representative that one or more Continuation Applications may have been filed from the '544 application. Should any such Continuation Applications be pending, Applicants will address the instant rejection to the degree it remains applicable when at least one of the co-pending applications is allowed.

Applicants note the provisional nature of the rejections for obviousness-type double patenting. Applicants submit that these rejections should be held in abeyance until at least one of

the co-pending applications is allowed. Applicants will address any obviousness-type double patenting issues in an appropriate fashion in any particular application once one or more of the group of copending applications is allowed.

Rejection for obviousness

The present claims 180-222 should not be deemed unpatentable under 35 U.S.C. § 103(a) as obvious over Belshe '036 in view of Collins '957 and Klein '207. As explained in the interview, Collins '957 is not available to the Examiner to make a rejection grounded on 35 U.S.C. § 103(a). 35 U.S.C. § 103(c). The present application was filed after November 29, 1999 and Collins '957 was assigned to the same entity, the Government of the United States of America as represented by the Department of Health and Human Services, as the present application was to be assigned at the time the present invention was made. This is evidenced by the eventual assignment of this application to that entity recorded at reel 011182, frame 0053 on September 25, 2000. Applicants' Representative notes that all of the inventors named on this application were employees of the National Institutes of Health and had an obligation, via an employment agreement, to assign their rights in the present invention to the Government of the United States of America as represented by the Department of Health and Human Services at the time the invention was made. Applicants will present evidence of such employment agreements at the request of the Examiner.

As was also explained in the interview, Klein '207 is not at all relevant to the present invention. Klein et al. describe making chimeric antigens, for example a chimera of a glycoprotein of a PIV with a glycoprotein of RSV, and then expressing the chimeric protein as a heterologous protein from a eukaryotic host cell in culture. See, for example, Examples 5-7, beginning at page 18 of the reference, describing expression of F_{PIV3}-F_{RSV} chimeric glycoprotein F from a baculovirus vector in Sf9 cells.

Such disclosure is not even remotely related to the present invention, in which a genome for a live, infectious, chimeric parainfluenza virus is constructed from the genomes of a bovine parainfluenza virus and a human parainfluenza virus. Other than perhaps providing description of what might be an interesting gene for an antigen to include in such a chimeric genome, Klein

'207 tells one of ordinary skill in the art nothing at all about any feature of the present invention, nor anything about how to make or use the present invention.

As to the Belshe reference, Applicants have previously argued that Belshe '036 is not enabling of its disclosed embodiments and Applicants maintain their view that such is the case. However, the USPTO has made clear, in this and other applications of the Applicants, their position that concession that Belshe is not enabling of its disclosure includes an admission that the reference does not enable its claims and would therefore be invalid and that such a finding will not be made without intercession of the Board of Appeals or other higher authority than the Examining Corps.

Thus, to advance prosecution of the present application, Applicants have presented new claims that make more clear the distinctions between the present invention and what is disclosed or suggested by Belshe.

The entirety of the Belshe '036 patent relies upon extrapolation from a single kind of experiment. That is, all of Belshe's speculation comes from the result of experiments in which growth of a cp45 strain of HPIV3 at various temperatures is complemented by a plasmid expressing one or more of the NP, P and L protein of the wild-type HPIV3. This experiment is summarized in the attached Exhibit 1.

HPIV3 strain cp45 was known to exhibit a temperature sensitive phenotype for replication, such that, at 39.5 °C, the replication of the virus is nil (see Table 1 at col. 6). Complementation by a plasmid expressing wild-type HPIV3 L protein provides some very small degree of recovery of virus plaques at the non-permissive temperature; about 300 or so plaques were formed, in comparison with the yield of 8×10^6 seen for the wild-type HPIV3 (compare Table 3 at col. 8 with Table 1 at col. 6).

Belshe concluded that the temperature sensitive replication phenotype of the cp45 virus was due to mutations in the L protein. From this single conclusion, Belshe et al. speculate about how a recombinant virus can be constructed.

Applicants have previously argued strenuously that Belshe does not establish any kind of expectation of success in making the "hybrid" viruses that he describes or in making the present

invention. However, as to the present claims, the Examiner should consider a few things about the Belshe reference.

First, the only genome described by Belshe et al. is a non-recombinant genome of the cp45 strain. Belshe et al. do not describe any sort of recombinant genome; they mention at col. 9, lines 64-66 that Example 7 "details methods for producing attenuated hybrid vaccines for target viruses...". However, Example 7 only provides citations of papers that describe the nucleic acid sequences of various viral genes. Belshe does state at the bottom of col. 8 that, "The gene sequence which encodes the surface glycoproteins of a target virus may be substituted for the corresponding sequence in the cp45 genome which codes for the HN and F proteins, to result in a hybrid virus." However, there is no further description of how this might be accomplished. At col. 9, lines 6-19, Belshe et al. describe that a hybrid virus should contain the 3' leader of cp45, NP, P[+C] and M proteins of cp45, a sequence encoding at least one surface glycoprotein of "an enveloped target virus" and "a variant protein which is different from the L protein of wild-type HPIV 3." All of the remaining disclosure of Belshe emphasizes that the L protein of any hybrid virus must be a variant from the wild-type L protein of cp45.

At the bottom of col. 6, Belshe et al. state that changes in the neuraminidase protein provide only minor decreases in replication, by less than a factor of 10, and therefore this protein is not a major factor in the attenuation of cp45. Belshe et al. also note that perhaps changes in the 3' leader sequence are "suspected in affecting the cold adaptive, temperature sensitivity and/or attenuation phenotypes of cp45." Thus, the only significant mechanism of attenuation that Belshe discloses or suggests is mutation of the L protein to a temperature sensitive phenotype by one or more point mutations.

To summarize, Belshe et al. only describe use of a cp45 genome or antigenome, having at least two of three defined point mutations in the L protein, to obtain an attenuated hybrid virus that contains the backbone of cp45, or at least the L protein of cp45, plus the surface glycoproteins of the heterologous target virus. The cp45 genome is a genome of a HPIV strain. Mutation of the L protein, and perhaps (though not definitively) in the 3' leader sequence, is the only mechanism of attenuation disclosed or suggested. Belshe et al. suggest that such an attenuated HPIV3 virus might be modified by substitution of its genes encoding the HN and/or F

glycoproteins with the corresponding genes from a "target virus" among those listed at col. 8, lines 42-58. However, as explained above, and in painstaking detail previously, Belshe et al. provide no disclosure whatsoever about how to accomplish such substitution.

On the other hand, the present claims recite that at least a certain degree (e.g. at least 10-fold) of attenuation is obtained by insertion of a gene or gene segments into the genome or antigenome of the chimeric virus, despite the presence of a gene encoding a wild-type L protein in the chimeric virus (claims 180, 203 and those dependent thereon). Alternatively, the present claims recite that the genome or antigenome of the chimeric virus includes a specific mutation in the L protein that provides at least a stated degree of attenuation (i.e. at least 10-fold; see claims 190, 213 and those dependent thereon). Neither of these possiblilities for attenuating a parainfluenza virus are disclosed or suggested by Belshe. Others of the present claims recite that a gene or gene segment of another virus is inserted into one or more specifically stated sites in the genome (or antigenome) of the chimeric virus (claims 181, 204 and those dependent thereon). Belshe describes only direct substitution of entire glycoprotein genes into their original positions. Belshe in no way describes insertion of any gene or gene segment into the sites recited in claim 181 or 204. Finally, some claims recite that the inserted sequence from another virus should be an open reading frame that is placed between gene start and gene end sequences that are operable in the "vector" virus genome or antigenome (claims 196, 218 and those dependent thereon) and that the result is attenuation by at least a stated degree (10-fold). Belshe et al. only test complementation of a HPIV3 mutant with HPIV3 wild-type L expressed from a plasmid, they do not disclose or suggest that a gene sequence of another virus should be expressed from regulatory sequences of the "vector" PIV, nor that such an arrangement of open reading frames and gene start and gene end signals could produce attenuation of viral replication.

For all of the reasons stated above, Belshe et al. do not disclose or suggest the instant invention. In fact, Belshe et al. teach away from the invention so claimed, at least as to claims 180, 197, 203, 219 and claims dependent thereon, which describe that attenuation is achieved despite the presence of a wild-type L protein gene in the chimeric viral genome or antigenome. Accordingly, the present claims 84-222 are both novel and unobvious over Belshe et al.

Klein '207 makes no disclosure that an infectious, chimeric PIV should incorporate a genome including any of the above-described features. Thus, combining Klein '207 with Belshe '036 does not remedy the deficiency of Belshe '036 to establish *prima facie* obviousness of the presently-claimed invention.

At least as to claims 180, 197, 203, 219 and claims dependent thereon, the Examiner may wish to consider in addition (or in the alternative) that the present specification presents results that may be taken as unexpected results obtained by the invention that demonstrate unobviousness in view of Belshe and Klein. In particular, as explained above, Belshe expressly states that a variant L protein including the particular mutations of cp45 is necessary for obtaining attenuation of a parainfluenza virus. However, the present specification, for example at Figure 11 and in the data of Tables 2 (p. 105), 10 (p. 126) and 13 (p. 137) describes results in which substantial attenuation of the infectious, chimeric PIV is obtained despite the presence of a wild-type L protein gene in the genome or antigenome of the chimeric virus.

For all of the above reasons, the instant claims 180-222 are novel and unobvious over Belshe '036 alone, or Belshe '036 in view of Klein '207. Accordingly, the rejection of claims 1-98 and 122-137 as either anticipated or obvious over these references should not be applied to the present claims.

The present application well-describes and claims patentable subject matter. The favorable action of allowance of the pending claims and passage of the application to issue is respectfully requested.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Mark J. Nuell (Reg. No. 36,623) at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

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Respectfully submitted,

By _____

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